IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CAREDX, INC.	)	
	)	
and	)	
	)	
THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,	)	C.A. No. 19-567 (CFC)
Plaintiffs,	)	**JURY TRIAL DEMANDED**
	)	
v.	)	
	)	
NATERA, INC.,	)	
	)	
Defendant.	)	

CAREDX'S OPPOSITION TO NATERA'S MOTION TO DISMISS

Dated: June 10, 2019

FARNAN LLP
Brian E. Farnan (Bar No. 4089)
Michael J. Farnan (Bar No. 5165)
919 N. Market St., 12th Floor
Wilmington, DE 19801
(302) 777-0300
(302) 777-0301 (Fax)
bfarnan@farnanlaw.com
mfarnan@farnanlaw.com

Edward R. Reines (admitted *pro hac vice*)
Derek C. Walter (admitted *pro hac vice*)
WEIL, GOTSHAL & MANGES LLP
201 Redwood Shores Parkway
Redwood Shores, CA 94065
(650) 802-3000

Attorneys for Plaintiffs

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I. NATURE AND STAGE OF THE PROCEEDINGS

On March 26, 2019, Plaintiff CareDx, Inc. ("CareDx") filed its Complaint alleging that Defendant Natera, Inc. ("Natera") infringes U.S. Patent Nos. 9,845,497 (D.I. 1-1, "the '497 patent") and 8,703,652 (D.I. 1-2, "the '652 patent;" collectively with the '497 patent, "the asserted patents"). On May 16, 2019, Natera moved to dismiss the Complaint. CareDx opposes. Additionally, CareDx respectfully requests that the Court set a scheduling conference while this motion is pending to avoid Natera achieving an unwarranted delay of this action.

II. SUMMARY OF THE ARGUMENT

As CareDx explained in its Complaint, the asserted patents protect inventive laboratory techniques that allow "doctors to assess [organ] rejection through blood tests and without invasive biopsies." D.I. 1, ¶ 1. These processes, which are reflected in the claims of the '497 and '652 patents, are the result of years of labor and innovation by eminent Stanford professor and researcher Dr. Stephen Quake and his co-inventors. Dr. Quake is a recognized pioneer in the biological sciences and known in particular for his innovative development of new precision measurement and diagnostic techniques for biological applications. *See* Exs. A and B.[1]

In 2009, Dr. Quake and his co-inventors pioneered new techniques for nucleic acid analysis and applied them to the field of organ transplants. They recognized an unmet need for non-invasive diagnostic tests for organ transplant rejection. While others had attempted to meet this need by utilizing a known linkage between concentrations of donor-specific, cell-free DNA[2] and organ rejection (what Natera apparently is identifying as the natural phenomenon),[3] Dr. Quake and

[1] Citations to "Ex." refer to exhibits to the concurrently filed Declaration of Derek C. Walter.
[2] For purposes of this brief, CareDx uses the term "DNA" to refer to deoxyribonucleic acid and all other nucleic acids, including ribonucleic acid (RNA).
[3] Natera is vague in what it identifies as the natural phenomenon in this case. But none of its varying formulations supports the invalidation of these claims based on Section 101.

his team recognized that the prior art attempts could be improved because they had utility only in limited circumstances, such as when a female recipient received an organ from a male donor, and lacked the sensitivity necessary to detect miniscule changes in concentrations of donor cell-free DNA. The inventors improved on these deficiencies through the use of innovative, highly precise assays capable of detecting tiny increases in donor-specific cell free DNA, thereby allowing doctors to recognize the onset of organ rejection before the damage becomes irreversible. These practical techniques are embodied in the claims of the asserted patents.

When Dr. Quake and his team were engaged in this innovative work, Natera did not even see this area as worthy of investigation. It was only years later, after the issuance of the asserted patents, that Natera decided to commercialize a "me-too" organ transplant rejection test. Rather than developing its own technology, Natera copied the processes developed by Dr. Quake and his colleagues years before. Now, faced with an infringement suit, Natera contends that the asserted patents should be summarily invalidated at the outset of the case because the very processes that it chose to copy supposedly add nothing to a long-known natural phenomenon. Not so, for at least the following reasons.

***First*,** the fact-intensive and technologically dense issues Natera's motion raises are wholly inappropriate for adjudication at the pleading stage. Natera's motion hinges on its assertion that the techniques recited in the asserted claims are well-known and conventional, which is an issue of fact that must be proven by clear convincing evidence. Natera's minimal evidentiary showing does not carry its heavy burden of proof under any circumstances, and does not remotely approach it here, given that every fact and inference must be construed in CareDx's favor.

***Second*,** there is nothing natural about the laboratory processes claimed in the asserted patents. On the contrary, the specific circumstances to which they relate—transplantation of an

organ from one person to another—are strikingly *unnatural*. Further, the specific sequence of steps that comprise the claimed methods, such as "genotyping a solid organ transplant recipient," and determining a concentration of donor-specific cell-free DNA by "detecting a homozygous or a heterozygous SNP" through the use of "high-throughput sequencing or digital polymerase chain reaction" assays, are the product of human ingenuity, not nature. In short, both the context for the use of the claimed method and the specific method steps themselves are the product of human ingenuity.

Third, the plain language of the claims and the specification of the asserted patents establish that the claims are directed to specific, concrete methods of detecting particular concentrations of donor-specific, cell-free DNA in the bodies of donor recipients, rather than—as Natera contends—some generalized correlation between donor-specific, cell-free DNA and organ rejection. Indeed, the specification teaches that the general idea that donor cell-free DNA could be used as an indicator of organ rejection was already known in the art, and that unsuccessful attempts had been made to develop practical protocols based on such an indication.

What was lacking, however, as the patents and the attached declaration of Dr. Henry Furneaux explain,[4] was the human ingenuity to develop a non-invasive procedure for measuring and utilizing this correlation that was reliably accurate and broadly effective for patients of all kinds. The methods claimed in the asserted patents satisfy this long-standing need, despite dark skepticism from researchers who had concluded, based on the shortcomings of then-existing methods, that "the use of plasma free DNA for the detection of organ rejection [is] difficult and

[4] Dr. Furneaux's declaration (and the other materials addressed in this opposition) are submitted to help the Court appreciate the technically and factually dense aspects of this request for judgment that make it improper as a pleading motion presented before the parties and the Court have had the benefit of fact and expert discovery. The declaration is not submitted to treat this motion as a proper pre-discovery summary judgment proceeding.

impractical." Ex. C at Abstract. In other words, prior artists were aware of the so-called correlation (the alleged natural phenomenon) and still could not invent a practical method of laboratory techniques to make it useful. *Id.* This proves that the invention is the product of human ingenuity rather than mere observation of a natural phenomenon. Natera's contention that the claims are directed to a natural phenomenon oversimplifies the claims, fails to evaluate them as an ordered combination, and ignores the patent's asserted advance over the prior art—all contrary to governing precedent.

Fourth, Natera's contention that the claims of CareDx's asserted patents are directed to natural phenomena is belied by its own actions and statements. In particular, Natera has filed, and continues to file, patent applications claiming processes similar to those that it argues here are merely directed to a natural phenomenon. *See, e.g.*, Exs. D, L. Similarly, Natera's marketing materials and press releases for its copy-cat organ transplant assay state that "[t]here is a great need for earlier, more precise non-invasive tools to assess allograft injury and rejection" and claim that "Natera's core single-nucleotide (SNP)-based massively multiplexed PCR (mmPCR) technology," which "works by measuring the fraction of donor-derived cell-free DNA (dd-cfDNA) in the recipient's blood," meets that need. Exs. E at 2 and F at 3. In other words, outside the context of this lawsuit, Natera characterizes methods for identifying donor-specific, cell-free DNA to monitor transplant status as proprietary, human-engineered "technology" that is properly the subject of patent applications. The Court should not allow Natera to avoid infringement of CareDx's innovative patents using a natural phenomenon defense, while it argues to the public and the Patent Office that the methods it has adopted for doing the same thing are innovative and patentable.

Natera's motion to dismiss should be denied.

III. STATEMENT OF FACTS

Organ transplants, or allografts, remain a relatively new and developing field of medicine. The first successful liver transplant occurred in 1963 and the first heart transplant in 1967. Furneaux Decl., ¶ 8. Over the ensuing decades, doctors have learned that the most important determinant of the success or failure of a transplant is whether, and the extent to which, the recipient's body "rejects" the transplanted organ and attacks it with its immune system. *See* '497 patent at 1:16-18, 7:7-39; *see also* Furneaux Decl., ¶¶ 8-9. Early detection of such rejection is crucial to the operation's success and patient survival. '497 patent at 6:8-28; Furneaux Decl., ¶ 9.

As the patents explain, however, as of 2009 conventional methods for monitoring the status of the recipient's immune response were invasive, expensive, and lacked necessary precision and sensitivity. *See* '497 patent at 5:58-6:61; *see also* Furneaux Decl., ¶ 10. Consequently, there had been "a major unmet medical need" for "early, non-invasive, safe, and cost-effective detection of acute rejection" for many years. '497 patent at 6:27-34; *see also* Furneaux Decl., ¶ 11. As the below language from Natera's website demonstrates, the inadequacy of conventional invasive methods for monitoring the status of transplanted organs is not in dispute:

> Assessing transplanted organ or "allograft" injury and rejection is a challenge with today's standard of care. Kidney biopsies are invasive and can be risky, costly and of variable quality. Blood tests measuring serum creatinine levels are often not accurate for assessing active rejection and require confirmatory invasive testing. Current standard of care can lead to patients with signs of allograft harm before the opportunity to treat. There is a great need for earlier, more precise non-invasive tools to assess allograft injury and rejection.

Ex. E at 2.

The inadequacy of these invasive monitoring methods has been known for decades. As early as the 1990s, researchers began to look to concentrations of circulating cell-free DNA as a possible source of a solution. Specifically, researchers recognized that the cell damage occurring during organ rejection would likely result in the presence of cell-free donor DNA in the recipient's

bloodstream and that, consequently, circulating cell-free DNA from a donor could serve "as a potential marker for the onset of organ failure." '497 patent at 8:9-29; Furneaux Decl., ¶ 11. Transforming this recognition in the community of the *potential* for donor circulating cell-free DNA to serve as an indicator of rejection into a usable clinical process that was effective for patients generally, however, proved challenging. '497 patent at 7:55-8:58; Furneaux Decl., ¶ 12.

Early efforts to use donor cell-free DNA as a marker for rejection focused on situations in which a female recipient received an organ from a male donor, which permitted researchers to focus on the presence of genes from Y-chromosomes in the recipient's blood stream (or other fluid sample). *See e.g.*, '497 patent at 7:55-8:29. The results were not promising even in this limited scenario. *See* Ex. C; *see also* '497 patent at 8:30-39; Furneaux Decl., ¶¶ 13-15. Indeed, so little progress was made that by 2008 researchers advocated abandoning cell-free DNA as a marker for rejection entirely: "***[T]he use of plasma free DNA for the detection of organ rejection [is] difficult and impractical***." Ex. C at Abstract (emphasis added).

Alternate efforts to utilize donor cell-free DNA focused on "detection of donor-specific human leukocyte antigen (HLA) alleles in circulating DNA…as a signal for organ rejection." '497 patent at 8:42-47. This path proved unsatisfactory, however, because of the "inability to distinguish HLA alleles between all donors and recipients, particularly for common HLA types," as well as other inherent obstacles identified in the art. *Id.* at 8:47-52; Furneaux Decl., ¶ 15.

As of 2009, no one had in fact developed a detection process that was effective for patients generally and real concerns about its practicality had been expressed. Furneaux Decl., ¶ 16. This unmet need in the art existed even though, years before the asserted patents were filed, the American Society for Nephrology "made the discovery and standardization of biomarkers for prediction, diagnosis, and prognosis of rejection the highest research priority." Ex. G at 2. This

status quo changed only as a result of the ground-breaking practical laboratory solutions for monitoring organ rejection pioneered by Dr. Quake and his team.

Dr. Quake's solutions built off of his pioneering work in the development of advanced genetic tools for nucleic acid analysis, such as high throughput sequencing and digital PCR. Indeed, during this time Dr. Quake started a company called Fluidigm, where he helped develop digital PCR technology, and another company called Helicos, where he developed novel high throughput sequencing techniques. *See* Ex. H. In 2009 the use of such approaches for quantifying tiny amounts of nucleic acids were certainly not routine, conventional, or well-understood as applied in the patents. Furneaux Decl., ¶¶ 12, 19. Indeed, many in the field at the time thought such tools were ***inappropriate*** for assessments of donor cell-free DNA concentrations. Furneaux Decl., ¶¶ 18-20.

Dr. Quake and his co-inventors, however, recognized that use of such high-precision, high-volume techniques, if implemented the right way, could and would facilitate improved detection and sampling of the tiny quantities of donor DNA present in an organ transplant recipient. *See*, *e.g.*, '497 patent at 17:4-35 (noting that, in typical situations, only "approximately one in 3,000 molecules analyzed will be from the donor and informative about donor genotype."); Furneaux Decl., ¶¶ 17-20. As the patents explain, "[c]ompared with the quantitative PCR techniques used in some of the earlier cited work, digital PCR is a much more accurate and reliable method to quantitate nucleic acid species including rare nucleic acid species, and does not require a specific gender relationship between donor and recipient." '497 patent at 15:10-15. This precision and reliability, in turn, made it practical to determine concentrations of donor-specific cell-free DNA via the innovative technique of comparing single nucleotide polymorphism profiles of the donor and the recipient. Furneaux Decl. ¶ 18; *see also* '497 patent at 11:33-63. This method, unlike

prior art methods that focused on Y-chromosome concentrations or HLA alleles, could be used for organ donor recipients generally. '497 patent at 8:30-58.

Natera had nothing to do with these technological achievements, and was focused on a different issue in 2009—prenatal genetic screening involving tests of fetal DNA. *See* Ex. I. Notwithstanding Natera's unsupported contention that all the steps of the methods claimed in the asserted patents are supposedly well-understood, conventional, and routine, Natera has been unable to launch its own competing non-invasive organ transplant rejection assay until just this year. *See* D.I. 1, ¶¶ 16-19, Ex. 3. This belated me-too product, however, relies upon the ground breaking inventions that Dr. Quake and his co-inventors described and claimed years ago. *Id.*, ¶¶ 20-25, Exs. 7-8. Despite relying on the methods claimed in the asserted patents, and despite its contention that such methods are directed to unpatentable natural phenomenon, Natera has described its competing transplant rejection assay as its "core technology." Exs. E and F. Not only that, Natera has filed late patent applications claiming similar processes for measuring the concentration of donor cell-free DNA in recipient fluid samples. *See* Ex. D.

IV. LEGAL STANDARDS

A. Legal Standard for Motion to Dismiss Under 12(b)(6)

In evaluating a motion brought under Rule 12(b)(6), the Court "must 'construe the complaint in the light most favorable to the plaintiff, and determine whether, under any reasonable reading of the complaint, the plaintiff may be entitled to relief.'" *M2M Sols. LLC v. Amazon.com, Inc.*, No. CV 17-202-LPS-CJB, 2017 WL 6294874, at *2 (D. Del. Dec. 11, 2017) (citation omitted). When, as here, a 12(b)(6) motion is based on the assertion of an affirmative defense, "dismissal is permitted only if the well-pleaded factual allegations in the Complaint, construed in the light most favorable to the plaintiff, suffice to establish the defense." *M2M Sols.*, 2017 WL 6294874, at *2. These standards apply with equal force to 12(b)(6) motions that allege

unpatentability under 35 U.S.C. § 101. *See Aatrix Software, Inc. v. Green Shades Software, Inc.*, 890 F.3d 1354, 1357 (Fed. Cir. 2018) ("If patent eligibility is challenged in a motion to dismiss for failure to state a claim pursuant to Rule 12(b)(6), we must apply the well-settled Rule 12(b)(6) standard which is consistently applied in every area of law.").

B. Legal Standard for Subject Matter Eligibility

The Supreme Court in *Alice Corp. Pty. v. CLS Bank Int'l.* confirmed that a two-step framework, first set forth in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66 (2012), applies to determinations of patent subject matter eligibility under 35 U.S.C. § 101. *See* 134 S. Ct. 2347, 2355 (2014). At *Alice* step one, a court must determine whether the claimed invention is "directed to" ineligible subject matter. *Alice*, 134 S. Ct. at 2354-55. This step requires a court to consider the claims "***in their entirety*** to ascertain whether their character as a whole is directed to excluded subject matter." *Internet Patents Corp. v. Active Network, Inc.*, 790 F.3d 1343, 1346 (Fed. Cir. 2015) (emphasis added). In making this determination, "[t]he Supreme Court has cautioned that 'too broad an interpretation of" ineligible subject 'could eviscerate patent law' because 'all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.'" *Endo Pharm. Inc. v. Teva Pharm. USA, Inc.,* 919 F.3d 1347, 1352–53 (Fed. Cir. 2019) (quoting *Mayo*, 566 U.S. at 71).

At *Alice* step two, a court must "examine the elements of the claim to determine whether it contains an 'inventive concept' sufficient to 'transform' the claimed abstract idea into a patent-eligible application." *Alice*, 134 S. Ct. at 2357. "Step two is 'a search for an inventive concept—i.e., an element or combination of elements that is sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the ineligible concept itself.'" *Intellectual Ventures I LLC v. Symantec Corp.*, 838 F.3d 1307, 1313 (Fed. Cir. 2016). "The 'inventive concept' may arise in one or more of the individual claim limitations or in the ordered combination of the

limitations" and establishing an absence of an inventive concept "requires more than recognizing that each claim element, by itself, was known in the art." *Bascom Glob. Internet Servs., Inc. v. AT&T Mobility LLC*, 827 F.3d 1350, 1349-1350 (Fed. Cir. 2016). "The question of whether a claim element or combination of elements is well-understood, routine and conventional to a skilled artisan in the relevant field is ***a question of fact***." *Berkheimer v. HP Inc.*, 881 F.3d 1360, 1368 (Fed. Cir. 2018) (emphasis added). "Any fact, such as this one, that is pertinent to the invalidity conclusion ***must be proven by clear and convincing evidence***." *Id*. (emphasis added).

V. ARGUMENT

A. *Alice Step One*: The Claims Of The Asserted Patents Are Directed To Specific Processes For Measuring Cell-Free Donor DNA, Not A Natural Phenomenon

1. Natera's Arguments Rely Upon A Legally Improper Oversimplification Of The Claims

The claims of the Asserted Patents bear no resemblance to the overbroad, non-specific claims that courts have invalidated under § 101. Rather than "simply stat[ing] [a] law of nature while adding the words 'apply it,'" *Mayo*, 566 U.S. at 72, the claims here are directed to specific processes for measuring and assessing concentrations of donor-specific, cell-free nucleic acids that—as discussed above—remedy the deficiencies of prior art methods and processes.

Those specific processes are reflected in the particular method steps recited in the claims collectively. Claim 1 of '497 patent, for example, is directed to "a method of detecting donor-specific circulating cell-free nucleic acids in a solid organ transplant recipient." The method requires the steps of (1) "genotyping a solid organ transplant donor to obtain a single nucleotide polymorphism (SNP) profile," (2) "genotyping a solid organ transplant recipient to obtain a SNP profile of the solid organ transplant recipient," (3) "obtaining a biological sample from the solid organ transplant recipient… wherein the biological sample comprises circulating cell-free nucleic acids from the solid organ transplant," and (4) "determining an amount of donor-specific

circulating cell-free nucleic acids from the solid organ transplant in the biological sample." '497 patent at 28:2-24. The SNP profile requirement alone differentiates it from prior art attempts to measure donor cell-free DNA. *See* '497 patent at 7:55-8:58; Furneaux Decl. ¶¶ 17-18.

The requirements of the human-developed techniques of the inventions do not stop there, however. The latter "determining" step must by performed in a particular way—"by detecting a homozygous or a heterozygous SNP within the donor-specific circulating cell-free nucleic acids." *Id.* at 28:25-26. Next, the detecting substep also must be performed in a particular way—through the use of one of two assays—high-throughput sequencing or digital polymerase chain reaction (dPCR). Finally, it is not enough that one of those two assays be used; the assay also must be sensitive enough to "detect[] the donor-specific circulating cell-free nucleic acids from the solid organ transplant when the donor-specific circulating cell-free nucleic acids make up at least 0.03% of the total circulating cell-free nucleic acids in the biological sample." *Id.* at 29:1-5.

Independent claim one of the '652 patent is, if anything, more specific. It not only requires genotyping to obtain a SNP profile, it also specifies that "at least one single nucleotide polymorphism (SNP) is homozygous for the subject if the genotype comprises subject-specific polymorphisms comprising SNP." '652 patent at 27:49-52. The claims also require a "multiplex sequencing" step and require detection sensitivity "greater than 56% compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy." *Id.* at 27:54 – 28:40.

The plain language of the claims thus squarely refutes Natera's unsupported assertion that the claims "begin and end with nucleic acids and their correlation to disease." D.I. 10 at 1. They are not directed to nucleic acids, any general correlation with disease, or anything else that could be characterized as a natural phenomenon. They are intended to be applied in the most unnatural circumstances—introduction of a foreign organ into a human body—and require a specific series

of complex laboratory techniques that are purely the result of human ingenuity. Furneaux Decl., ¶¶ 21-23. That the claims merely involve or relate in some way to the effects of the body's immune response on donated organs, without more, is far from establishing unpatentability. *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1050 (Fed. Cir. 2016) ("[I]t is not enough to merely identify a patent-ineligible concept underlying the claim; we must determine whether that patent-ineligible concept is what the claim is 'directed to.'").

Here, Natera's contention that the claims are "focused on nothing other than natural phenomena" relies on a sloppy oversimplification of the claims, in precisely the manner that the Supreme Court and Federal Circuit have warned against. *See Endo,* 919 F.3d at 1352–53 ("The Supreme Court has cautioned that 'too broad an interpretation of" ineligible subject matter 'could eviscerate patent law' because 'all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.'" (quoting *Mayo*, 566 U.S. at 71)); *McRo, Inc. v. Bandai Namco Games America, Inc.*, 837 F.3d 1299, 1313 (Fed. Cir. 2016) ("We have previously cautioned that courts 'must be careful to avoid oversimplifying the claims' by looking at them generally and failing to account for the specific requirements of the claims."). Indeed, Natera's *Alice* step one analysis ***literally reads out*** all of the core method steps of the claims. *See* D.I. 10 at 10-11 (analyzing only the initial and final limitations of claim 1 of each asserted patent). This is an error of law. *See, e.g.*, *Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327, 1338 (Fed. Cir. 2016) (reversing unpatentability finding because "district court oversimplified the self-referential component of the claims and downplayed the invention's benefits"). Indeed, if Natera's own recently filed patent applications were evaluated in this overly simplistic manner, they would plainly be rejected on natural law grounds. *See* Ex. D (claiming a "method for determining transplant status" that begins with the step of "obtaining a nucleic acid sample" and

ends with "determining a transplant status based on the measured amount of transplant cell-free DNA").

When the actual limitations of the claims are evaluated, it is plain that Natera's assertion that "[t]hese claims parallel those found ineligible in *Mayo*, *GeneticTechs.*, and *Ariosa*" (D.I. 10 at 11) is groundless. As the table in Appendix A demonstrates, none of the claims held unpatentable in those cases were remotely similar to the specific, complex processes claimed in the '497 and '652 patents. As discussed above, the asserted claims here do not begin with natural phenomena and, even if they could be characterized in that way, the specific, unconventional claim steps that follow establish that they are directed to specific laboratory techniques. Further, as the Federal Circuit has recognized, "[i]n *Ariosa*, like *Mayo*, there was no dispute that the claimed methods were well-known, routine and conventional." *Exergen Corp. v. Kaz USA, Inc.*, 725 F. App'x 959, 967 (Fed. Cir. 2018). Here, in contrast, as is apparent from the factual background discussion above, Natera's unsupported assertions about the purportedly conventional nature of the method steps are very much in dispute.

Indeed, the challenged claims recite a series of specific, non-conventional laboratory techniques for detecting cell-free DNA with a high degree of sensitivity, in a manner that improves upon prior art methods of attempting such detection. Furneaux Decl., ¶¶ 11-20. This places them squarely in the category of claims that the Federal Circuit has upheld. *See CellzDirect*, 827 F.3d at 1048 ("It is enough in this case to recognize that the claims are simply not directed to the ability of hepatocytes to survive multiple freeze-thaw cycles. Rather, the claims of the '929 patent are directed to a new and useful laboratory technique for preserving hepatocytes").

2. Natera Fails to Address the Claimed Improvement Over The Prior Art or Preemption

The *Alice* step one analysis must include an evaluation of the patent's "claimed advance" over the prior art. *See Finjan, Inc. v. Blue Coat Sys., Inc.*, 879 F.3d 1299, 1303 (Fed. Cir. 2018) ("Starting at step one, we must first examine the '844 patent's 'claimed advance' to determine whether the claims are directed to an abstract idea." (citing *Affinity Labs of Tex., LLC v. DIRECTV, LLC*, 838 F.3d 1253, 1257 (Fed. Cir. 2016)). Natera's truncated analysis neglects this entirely. Indeed, Natera's step one analysis fails to *even mention*, much less substantively address, the asserted patents' extended discussion of prior, unsatisfactory attempts to develop diagnostic tests using cell-free donor DNA; attempts that were so unsuccessful as to prompt some in the field to give up on cell-free DNA as a rejection marker entirely. Ex. C at 1. The specification's discussion of these attempts, which must be accepted as true and construed in CareDx's favor, shows that existing non-invasive techniques that used cell-free DNA were ineffective, and that the broad applicability of the claimed methods to patients generally was a core advance over such prior art methods: "[i]n some embodiments, the ***invention provides a universal approach to noninvasive detection of graft rejection*** in transplant patients which…***is general for all organ recipients without consideration of gender***." '497 patent at 8:53-58 (emphasis added). The patent does not assert or suggest that the inventors discovered the relationship between cell-free DNA concentrations and transplant rejection, and does not purport to claim such a relationship. Instead, it expressly acknowledges unsatisfactory prior art attempts to harness the relationship, and proposes specific, concrete—and thus patentable—processes for doing so that depart from the failed approaches used in the prior art. *See CellzDirect*, 827 F.3d at 1049 (claims patentable at *Alice* step one in part because claimed process produces results that are "new and vastly more useful" than those "made by conventional methods"). Natera does not address these advances over

the prior art, and should not be heard to contest their importance to the patentability inquiry since it has represented to the Patent Office that "significantly improved results" attributable to its alleged inventions were enough to defeat a Section 101 rejection. Ex. L at 5.

Nor does Natera address "the primary concern driving § 101 jurisprudence"—preemption. *McRO,* 837 F.3d at 1314. With good reason, since it is plain from both the language of the claims themselves, and the specification's discussion of prior, inferior attempts to use cell-free DNA as an indicator of transplant rejection, that the asserted claims do not preempt development of other, alternative methods. That Natera itself continues to file patent applications claiming methods for using cell-free DNA as a biomarker of transplant rejection, applications that it presumably believes are novel and non-obvious over the asserted patents, confirms that no preemption in fact exists.

In short, Natera's conclusory analysis at step one fails to address the actual language of the claims, which show that the claims of the asserted patents are directed to specific, novel processes for detecting donor-specific cell free DNA, fails to address the patent's express statements regarding the improvements the claimed methods provide over the prior art, and fails to analyze the central issue underlying the judicial exceptions to patentability. Under these circumstances, the Court need proceed no further—the claimed methods are not "directed to" any natural phenomena, and the Court should deny Natera's motion on that basis at the outset.

B. *Alice Step Two*: The Claims Include an Inventive Combination of Steps

1. Natera's Arguments Rest On Mischaracterizations Of The Claim Language And Specification

Natera's step two arguments are scarcely more detailed than its cursory arguments at step one. Once again, Natera simply ignores the portions of the specification that explain how the claimed methods greatly improve upon prior art non-invasive techniques involving measurements of cell-free DNA. *See, e.g.*, '497 patent at 7:55-8:63. Instead, Natera addresses (at a very high

level) individual limitations in isolation—without regard to the role they play in the invention as a whole or to the nature of the claimed advance over the prior art—and concludes that each is well-understood and conventional (or in some cases, reversing the appropriate burdens as will be discussed below, that the patent does not affirmatively describe the technique in question as non-conventional). This approach fails on multiple levels.

First, Natera is wrong on the facts even as to the individual claim limitations when viewed in isolation. Natera touts general specification language suggesting that the invention employs conventional techniques, while ignoring that the same language cautions that such techniques are only used "***unless* otherwise indicated**." D.I. 10 at 12 (emphasis added). Here, the plain language of the claims establish that performance of the claimed methods requires use of non-conventional processes and techniques. All claims of the '497 patent, for example, require the use of high-throughput sequencing or dPCR assays. As Dr. Furneaux explains, however, neither of these types of assays were well-known or conventional to be used this way. Furneaux Decl., ¶ 19.

Natera's specification citations are not to the contrary, and do not stand for what Natera contends they do. For example, Natera asserts that the patent discloses that the high-throughput analysis/dPCR limitation "can be accomplished through classic Sanger sequencing methods which are ***well known in the art***." D.I. 10 at 13 (quoting, with added emphasis, '497 patent at 15:27-33). This is the opposite of what the patent says. In actuality, the patent ***contrasts*** the "classic Sanger sequencing methods" with "high-throughput systems" and explains they are mutually exclusive alternatives. '497 patent at 15:27-33. Notwithstanding that high-throughput analysis was known in the art, it was certainly not conventional to use it for the purposes described and claimed in the asserted patents. Furneaux Decl., ¶¶ 17-20, 24-25; *see also Berkheimer*, 881 F.3d at 1369 ("Whether a particular technology is well-understood, routine, and conventional goes beyond what

was simply known in the prior art."). Further, with respect to digital PCR, the patent expressly touts it as s*uperior* to methods used in the prior art. '497 patent at 15:10-15 ("Compared with the quantitative PCR techniques used in some of the earlier cited work, digital PCR is a much more accurate and reliable method to quantitate nucleic acid species including rare nucleic acid species, and does not require a specific gender relationship between donor and recipient.").

With respect to the sensitivity limitations in both asserted patents, Natera merely states that "[t]here is no assertion or evidence that these techniques – or sensitivities that naturally result from their use – is unconventional or new." D.I. 10 at 14. This turns the applicable burdens on their head. "Whether the claim elements or the claimed combination are well-understood, routine, and conventional is a question of fact." *Aatrix*, 882 F.3d at 1121. Accordingly, it is Natera's burden to prove, by clear and convincing evidence, that all individual limitations (and the claimed combination as a whole, as is discussed below) are well-known and conventional. *See Berkheimer*, 881 F.3d at 1368. It has not come remotely close to doing so, and its step two arguments fail as a matter of law for that reason alone.

Second, even assuming that each of the individual limitations were known and conventional (and they are not, as set forth above), Natera's approach is directly contrary to established precedent holding that the *Alice* step two analysis requires evaluation of whether the claimed invention ***as a whole*** can be characterized as well-understood or conventional—precedent that Natera has repeatedly pointed out to the Patent Office in arguing for the patentability of its own claims. *See* Ex. L at 2-4, 8-10. The Federal Circuit's analysis in *Bascom* is instructive on this point: "The inventive concept inquiry requires more than recognizing that each claim element, by itself, was known in the art. As is the case here, an inventive concept can be found in the non-conventional and non-generic arrangement of known, conventional pieces." 827 F.3d at 1349–50.

Here, Natera fails to meaningfully engage in this required analysis. Instead, it falls back on its (incorrect) assertion that all the constituent limitations of the claims are well-known and conventional. *See generally* D.I. 10 at 17-19. Nowhere does it mention, much less analyze, the patents' own express statements about how the claimed invention provides advantages over the prior art. These statements, which must be accepted as true at this stage, conclusively establish that the claimed methods—when viewed as an ordered combination—are not conventional or well-known. To the extent that the Court reaches step two of the *Alice* inquiry, Natera's motion should be denied for this independent basis.

2. Prior Art Failures and the Patent Office's Related Findings Establish That The Claimed Methods Are Inventive

The prior art deficiencies recounted in the patents and described above further establish that the claimed methods include an inventive concept. As the patents explain, the potential for cell-free DNA to serve as an indicator of rejection was known at least as early as 1998. '497 patent at 7:60-65. Yet over the ensuing eleven years, despite repeated attempts and high levels of interest in the potential for cell-free DNA as an indicator of organ rejection, no one but the inventors of the asserted patents came up with a way to utilize the alleged natural phenomenon that was effective for patients generally. Not only that, but—as the Vymetalova paper cited in the patents demonstrates—the shortcomings of conventional methods for measuring cell-free DNA led some researchers in 2008 to ***affirmatively dismiss*** cell-free DNA as a viable indicator of organ rejection. Ex. C at 1 ("***[T]he use of plasma free DNA for the detection of organ rejection [is] difficult and impractical***."); *see also* Furneax Decl. ¶¶ 13, 16. That Dr. Quake and his team achieved a solution to this long-felt but unmet need despite the outright skepticism of others in the field is a testament to the inventiveness of the laboratory techniques to perform the test method.

The file histories of the asserted patents confirm this. Both patents were examined after the Supreme Court's *Alice* and *Mayo* decisions; their allowance thus represents the Patent Office's judgment that they satisfy the patentability standards set forth in those cases. Further, the Patent Office considered hundreds of prior art references and made specific factual findings that led to the allowance of the claims. With respect to the '497 patent, for example, the examiner found that one leading reference does "not teach homozygous or heterozygous polymorphisms," while another does not teach "determining an amount of donor-specific cell free DNA from a solid organ transplant.'" Ex. J at 27. With respect to obviousness, the examiner found that "one of ordinary skill in the art at the time the invention was made would not have a reasonable expectation of success in detecting at least 0.03% of donor specific circulating cell-free nucleic acids in the blood, serum or plasma of the solid organ transplant recipient." *Id.* at 36. Similarly, during the '652 patent prosecution the examiner found that a long series of prior art references, including many that disclosed methods of utilizing donor cell-free DNA as an indicator of rejection, failed to disclose the specific, inventive steps recited in the claims. Ex. K at 3. Natera has presented no evidence to rebut these findings of fact, much less the clear and convincing evidence the law requires, and thus the Court should decline Natera's invitation to substitute its judgment for that of the Patent Office at the pleading stage, without the benefit of a full evidentiary record.

C. The Court Should Reject Natera's Inappropriate Attempt To Dismiss Caredx's '652 Patent Claim Based On A Misreading Of The Claims

Natera's argument that CareDx's '652 patent infringement claims should be dismissed is premature and amounts to an improper attempt to short-circuit this Court's discovery and claim construction processes. *See United States Gypsum Co. v. New NGC, Inc.,* No. 17-130, 2017 WL 5187845, at *3 (D. Del. Aug. 18, 2017) (denying motion to dismiss based on purportedly implausible allegations of direct infringement, and stating that "the court does not address the

merits of an infringement claim at this point in the case"); *Internet Media Corp. v. Hearst Newspapers, LLC,* No. CIV. 10-690-SLR, 2011 WL 2559556, at *3 (D. Del. June 28, 2011) (denying 12(b)(6) motion because "defendant's motion would require the court to construe said claims, an action that is not appropriate in connection with a motion to dismiss"). Construing all facts and resolving all inferences in CareDx's favor, as the procedural posture requires, CareDx has more than plausibly alleged infringement of the '652 patent.

Specifically, Exhibit 8 to CareDx's Complaint, which the Complaint expressly incorporates by reference and states should be treated as part of the pleading (D.I. 1 at ¶ 37), provides ample exemplary evidence regarding the sensitivity of Natera's accused products. D.I. 1-8 at 6-8. The sensitivity levels cited range from 91.8% to 89%. *Id.* It is entirely plausible that these high sensitivities are "greater than 56% compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV)," and Natera has presented no evidence to the contrary. Natera's dismissal argument is predicated on its bare assertion that sensitivity figures for heart transplants are "unrelated to," and cannot be compared with sensitivity figures for kidney transplants, (D.I. 10 at 19), but the Court has no factual basis for crediting that attorney argument.

Further, both Natera's direct infringement and DOE arguments rely upon an unduly narrow, unsupported claim construction theory—that the claim requires *actual performance of a comparison*, as opposed to merely requiring sensitivity that is in fact greater than 56% compared to the specified methods. *See* D.I. 10 at 20 ("Natera does not compare the sensitivity of its Kidney Test to ***anything*** when performing it" (emphasis in original)). This claim construction argument has no place at the pleading stage. *See, e.g.*, *Internet Media*, 2011 WL 2559556, at *3. Natera's motion should be denied.

VI. CONCLUSION

For the foregoing reasons, Natera's motion to dismiss should be denied with prejudice.

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Respectfully submitted,

FARNAN LLP

/s/ Brian E. Farnan

Brian E. Farnan (Bar No. 4089)
Michael J. Farnan (Bar No. 5165)
919 N. Market St., 12th Floor
Wilmington, DE 19801
(302) 777-0300
(302) 777-0301 (Fax)
bfarnan@farnanlaw.com
mfarnan@farnanlaw.com

Edward R. Reines (admitted *pro hac vice*)
Derek C. Walter (admitted *pro hac vice*)
WEIL, GOTSHAL & MANGES LLP
201 Redwood Shores Parkway
Redwood Shores, CA 94065
(650) 802-3000

Attorneys for Plaintiffs